AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 01: Arthritis and Nontraumatic Joint Disease

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 750 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists four topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before November 6, 2015, in this priority area; and (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Seventeen topics in this priority area were being tracked in the system as of November 6, 2015.) All four topics emerged as having potential for high impact on the basis of experts' comments and their assessment of potential impact. These are listed in the table below. The material on interventions in this Executive Summary and report is organized alphabetically by disease state. Readers are encouraged to read the detailed information on the interventions that follows the Executive Summary.

Priority Area 01: Arthritis and Nontraumatic Joint Disease

Topic	High-Impact Potential
1. Baricitinib for treatment of rheumatoid arthritis	High
2. Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout	Moderately high
3. Secukinumab (Cosentyx) for treatment of ankylosing spondylitis	Moderately high
4. Secukinumab (Cosentyx) for treatment of psoriatic arthritis	Moderately high

Discussion

Eligible Topics Deemed High Impact

Arthritis and nontraumatic joint disease is a priority area in which we have identified a moderate number of interventions as meeting criteria for tracking in the Healthcare Horizon Scanning System. Experts deemed four topics as having high-impact potential: An oral drug for treating rheumatoid arthritis (RA), an oral drug for treating gout, and a monoclonal antibody for treating either ankylosing spondylitis (AS) or psoriatic arthritis (PsA).

Ankylosing Spondylitis

Secukinumab (Cosentyx) for Treatment of Ankylosing Spondylitis

- **Key Facts:** AS is an inflammatory form of arthritis that primarily affects the spine and can cause vertebrae to fuse; no cure exists. Treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) are used for first-line therapy to treat AS pain; additionally, corticosteroids and biologic tumor necrosis factor (TNF)-alpha inhibitors may also be prescribed. However, these treatment options are not effective for about 40% of patients with AS. Secukinumab (Cosentyx™) is a monoclonal antibody antagonist targeting interleukin-17A (IL-17A), a cytokine thought to be involved in developing delayed-type hypersensitivity reactions. This effect is reported by investigators to be mediated by increased chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17A–localized autoimmune reactions, AS pathogenesis could be reduced while minimizing the systemic immunosuppression associated with TNF-inhibitor therapy. In clinical trials, secukinumab has been administered as a series of 3 or 4 loading doses, intravenously or subcutaneously, followed by 1 subcutaneous injection (75 or 150 mg) once every 4 weeks.

  Five phase III trials are ongoing of secukinumab for treating AS. Investigators have reported data from two of these clinical trials showing that more patients treated with secukinumab achieved Assessment in Ankylosing Spondylitis 20 (ASAS20) rates than patients given placebo. Patients with AS who did not respond to prior treatment with TNF therapies showed significant improvement in ASAS20 rates with secukinumab, although these rates were significantly lower than in patients who were treatment-naïve. Treatment benefit continued at 52 and 104 week followup in some patients. However, patients given secukinumab were more likely to experience adverse events, including serious events, than patients given placebo.

  In September 2015, secukinumab's manufacturer reported that it had submitted global regulatory filings for secukinumab for treating AS, as well as for treating PsA. In January 2015, the U.S. Food and Drug Administration (FDA) approved secukinumab for treating the skin condition plaque psoriasis.

  Because secukinumab has been approved for treating plaque psoriasis, the cost of the drug is available. As of November 2015, the retail cost of a single 150 mg pen-injector of secukinumab was reportedly about $3,900, which could be administered once every 4 weeks for treating AS. If approved for treating AS, secukinumab would likely be covered by third-party payers for treating patients with active AS who have had an inadequate response to two or more NSAIDs or patients who have had an inadequate response to a biologic TNF inhibitor.
- **Key Expert Comments:** Experts commenting on this intervention stated that a significant unmet need exists for patients with AS whose condition fails to respond to treatment with existing therapies. However, the experts wanted to see additional clinical studies that compare the efficacy of secukinumab to TNF inhibitors as well as to determine long-term efficacy. High treatment costs could limit patient access if third-party payers do not cover the drug.

High-Impact Potential: Moderately high

Gout

Lesinurad for Treatment of Hyperuricemia and Allopurinol-Refractory Gout

- **Key Facts:** Gout is the most prevalent form of inflammatory arthritis and is associated with impaired health outcomes and worsened quality of life. According to data from the U.S. National Health and Nutrition Examination Survey 2007–2008, about 8.3 million adults have gout. Patients with gout have elevated serum uric acid (sUA) levels, which can result in monosodium urate crystals forming and depositing in and around joints, leading to acute flares and inflammation. Uncontrolled gout can lead to accumulation of pockets of urate crystals called tophi, which cause chronic pain, joint erosion, and limited mobility. Current treatment options for reducing hyperuricemia in patients with gout include the xanthine oxidase inhibitors allopurinol and febuxostat, which decrease uric acid production. Hyperuricemia is believed to be the most important risk factor for developing gout. About 47% of patients with gout do not achieve target goals for sUA levels (<6 mg/dL) with the standard of care, allopurinol or febuxostat. Only about 30% of patients achieve overall gout control, so a significant unmet need exists for more effective treatments. About 90% of patients with gout are thought to have insufficient excretion of uric acid due to genetic defects in renal transporters of uric acid, including the human urate transporter 1 (URAT1), which is involved in uric acid reabsorption. By selectively inhibiting URAT1, lesinurad is thought to promote urinary excretion of uric acid, leading to improvements in hyperuricemia. In clinical trials, lesinurad 200 mg or 400 mg has been administered orally, once daily, as monotherapy or in combination with a xanthine oxidase inhibitor in patients with gout-related hyperuricemia.

  Five phase III trials on lesinurad have been completed, and two phase III extension trials are ongoing. In phase III clinical trials, significantly more patients treated with lesinurad in combination with a xanthine oxidase inhibitor achieved target sUA levels than patients given a xanthine oxidase inhibitor alone. Additionally, with lesinurad monotherapy, more patients with gout and an intolerance or contraindication to xanthine oxidase inhibitors achieved target sUA levels than did those given placebo. Patients given lesinurad as monotherapy were more likely to experience serum creatinine elevations and renal adverse events, including serious events, than patients given placebo. Other adverse events commonly reported in patients treated with lesinurad monotherapy included constipation, diarrhea, and nausea. When lesinurad was combined with xanthine oxidase inhibitors, commonly reported adverse events were arthralgia, back pain, nasopharyngitis, and upper respiratory tract infection.

  The company has filed FDA regulatory submissions for lesinurad given as 200 mg once-daily combination therapy with a xanthine oxidase inhibitor for treating gout; a decision date is set for December 29, 2015. The manufacturer does not intend to pursue FDA approval of lesinurad as a monotherapy.

  Our searches found no information regarding the expected cost of lesinurad. However, one financial analyst predicted annual sales of lesinurad could reach $582 million by the year 2020. An estimated 10% of patients with chronic gout could be prescribed lesinurad, according to an April 2012 survey of rheumatologists in the United States performed by health care consultant Decision Resources Group. If approved, lesinurad would be covered by third-party payers similar to other uric acid–lowering drugs for treating or preventing gout, although if the drug is more costly than alternatives, prior authorization and a tiered approach would likely be used.

- **Key Expert Comments:** Experts commenting on this intervention stated that a significant unmet need exists for new treatment options to help patients with gout improve their sUA levels. Many treatment options are available to address acute flares and manage chronic gout. However, the experts noted that few agents are available to address the underlying mechanisms leading to gout, including uric acid underexcretion. Lesinurad, which increases uric acid excretion, demonstrates potential for reducing sUA levels in combination with xanthine oxidase inhibitors. However, the experts warned that lesinurad uptake could be limited by concern about adverse events, such as kidney complications, which will continue to be elucidated in ongoing clinical trials. The drug's long-term safety may also affect its adoption.
- **High-Impact Potential:** Moderately high

Psoriatic Arthritis

Secukinumab (Cosentyx) for Treatment of Psoriatic Arthritis

- **Key Facts:** PsA is a form of chronic inflammatory arthritis that affects people with the skin condition psoriasis. In about 80% of patients, the skin condition develops before arthritis; its exact cause is unknown. The National Psoriasis Foundation estimates about 7.5 million Americans have psoriasis, of whom 10% to 30% will also develop PsA. The main symptoms of PsA are joint pain, stiffness, and swelling that can affect any joint. Symptoms worsen over time, with periods of improvement or remission. Severe PsA will develop in a small proportion of patients, appearing in their hands, feet, and spine, which can lead to deformities and disability. In patients with severe PsA, early treatment is essential to achieve optimal pain relief and to prevent joint destruction. Current treatments focus on reducing inflammation, improving mobility, and decreasing pain. Some patients' symptoms do not respond adequately to treatment with NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs) or TNF inhibitors; suggesting other treatment options are needed. Secukinumab is a monoclonal antibody antagonist for interleukin-17 (IL-17A). IL-17A is a cytokine believed to be involved in developing delayed-type hypersensitivity reactions by increasing chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17A–localized autoimmune reactions, PsA symptoms may be limited while minimizing the systemic immunosuppression associated with TNF blockers. In clinical trials, secukinumab has been administered as a series of 3 loading doses, 10 mg/kg, intravenously, followed by 1 subcutaneous injection (75 mg) once every 4 weeks; secukinumab was also administered as 1 subcutaneous loading dose (75, 150, or 300 mg) followed by the same dose, subcutaneously, once weekly over 4 weeks.

  Five phase III trials on secukinumab for treating PsA are ongoing. In phase III trials, patients treated with secukinumab yielded a significant improvement in American College of Rheumatology ACR20 response rates versus placebo. This improvement was observed in both TNF-naïve and TNF-refractory populations. Treatment benefit continued up to 52 or 104 weeks in some patients. However, patients given secukinumab were more likely to experience adverse events, including serious adverse events, than patients given placebo. The most common adverse events reported in patients with PsA taking secukinumab were headache and upper respiratory tract infection.

  FDA approved secukinumab in January 2015 for treating plaque psoriasis; global regulatory filings for secukinumab for treating PsA, as well as AS, were submitted in the second half of 2015.

Because secukinumab is approved for treating plaque psoriasis, its cost is available for that indication. As of November 2015, the retail cost of a single 150 mg pen-injector of secukinumab was reportedly about $3,900, which could be administered once every 4 weeks for treating PsA. If approved for treating PsA, secukinumab would likely be covered by third-party payers, and require prior authorization; patients with PsA who have had an inadequate response to one or more conventional or biologic DMARDs may be considered for coverage.

- **Key Expert Comments:** Overall, experts commenting on secukinumab stated that the drug could potentially fill an unmet need for patients with PsA whose disease does not respond to available therapies. However, the experts thought that more clinical studies are needed to determine the long-term efficacy of secukinumab, as well as to compare its efficacy to that of existing therapies such as TNF inhibitors. High cost could limit patient access to the drug. However, these costs may be offset by decreased use of other health care resources.
- **High-Impact Potential:** Moderately high

Rheumatoid Arthritis

Baricitinib for Treatment of Rheumatoid Arthritis

- **Key Facts:** RA is a chronic autoimmune disease that causes inflammation of joints and surrounding tissues and can also affect other organs. RA is prevalent in an estimated 0.5% to 1.0% of the general population. In 2005, 1.5 million U.S. adults had RA, which represented a decrease from 2.1 million U.S. adults in 1999. An estimated 41 new cases per 100,000 people occur each year in the United States. In patients with RA, the immune system attacks the synovial membranes that line the joints. Symptoms include morning stiffness; tender, warm, or swollen joints; joint pain; loss of range of motion; and deformed joints. Early diagnosis of RA (within 6 months of onset) is essential to optimize treatment outcomes and slow disease progression. A cure does not exist; patients typically require lifelong treatment, although early and aggressive intervention can delay joint deterioration. Current treatments for RA focus on reducing inflammation, improving mobility, and decreasing pain. Some patients' symptoms do not respond adequately to treatment with NSAIDs, conventional DMARDs such as methotrexate, or biologic DMARDs such as TNF inhibitors. Baricitinib inhibits Janus kinases (JAK) 1 and 2, which are thought to be involved in RA pathogenesis. Blocking the activity of JAKs may reduce the activity of downstream, pro-inflammatory effector cytokines including granulocyte-macrophage colony stimulating factor, interleukin (IL)-6, IL-12, IL-15, IL-23, and interferon gamma.

  Two phase III trials on baricitinib for treating RA are ongoing, including one long-term extension study in patients who previously received baricitinib. In phase III trials, patients treated with baricitinib had a significant improvement in ACR20 responses versus patients treated with placebo and patients treated with methotrexate or the TNF-inhibitor adalimumab. These improvements were observed in both DMARD-naïve and DMARD-refractory populations, although the greatest improvements were seen in DMARD-naïve patients. Occurrence of adverse events, including serious events, was similar in patients given baricitinib or placebo. The most common adverse events reported for baricitinib were headache, nasopharyngitis, and upper respiratory tract infection; no opportunistic infections occurred.

  Data from ongoing trials are expected to be available in 2016, which may be used to support regulatory filings. The drug's manufacturer has not yet announced plans to submit these filings to FDA.

Because baricitinib is not approved for treating RA, no cost information is available. If approved for treating RA, baricitinib would likely require prior authorization by third-party payers, including documentation that patients with RA had an inadequate response to methotrexate or a biologic DMARD before being eligible for baricitinib.

- **Key Expert Comments:** Of note, data from clinical trials comparing baricitinib to conventional or biologic DMARDs were released in November 2015, and were not available at the time that we solicited expert comments on this intervention. Therefore, experts have reviewed only data comparing baricitinib to placebo; the recent data may improve experts' opinions of baricitinib because the new data addressed some of the concerns. Overall, experts commenting on baricitinib stated that the drug could potentially fill an unmet need for patients with RA whose disease does not respond to available therapies. Baricitinib will be significantly more expensive than conventional DMARDs, thought experts, and patient access to the drug may be limited if third-party payers do not cover the majority of treatment costs. However, these costs may be offset by decreased use of other health care resources used for treating RA.
- **High-Impact Potential:** High

Ankylosing Spondylitis Intervention

Secukinumab (Cosentyx) for Treatment of Ankylosing Spondylitis

Unmet need: Ankylosing spondylitis (AS) is a form of autoimmune arthritis that primarily affects the spine and can cause vertebrae to fuse. Up to about 1% of the general population is affected by AS, with a higher distribution in people of European descent.[1] No cure exists. Up to 70% of patients with severe AS can develop spinal fusion, and up to 40% of patients do not respond to the treatment options of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), or tumor necrosis factor (TNF) inhibitors, representing a substantial unmet need for additional therapeutic options for patients with AS.[2]

Intervention: Secukinumab is a fully human monoclonal antibody antagonist for interleukin-17 (IL-17A). IL-17A is a cytokine believed to be involved in developing delayed-type hypersensitivity reactions. These effects are thought to be mediated by increased chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17A–localized autoimmune reactions, AS pathogenesis could be purportedly reduced while minimizing the systemic immunosuppression associated with TNF blockers, which are the only biologic agents used for reducing AS-associated inflammation.[2] In phase III trials, secukinumab was administered as 3 loading doses of an intravenous (IV) infusion 10 mg/kg at baseline, 2 weeks, and 4 weeks, followed by 1 subcutaneous (SC) injection (75 mg or 150 mg) every 4 weeks;[3] or secukinumab was administered as 3 weekly loading doses (75 mg or 150 mg) administered subcutaneously at weeks 1, 2, 3, and 4, followed by a dose every 4 weeks.[4]

Clinical trials: Preliminary data are available for two ongoing clinical trials evaluating secukinumab in patients with active AS. In the phase III MEASURE 1 trial, patients (n=371) with active AS who were intolerant of or did not respond to NSAIDs, DMARDs, or TNF inhibitors, were treated with secukinumab. The drug was administered in 3 loading doses as an IV infusion, 10 mg/kg, at baseline, 2 weeks, and 4 weeks, followed by one SC injection (75 or 150 mg) every 4 weeks. Patients receiving secukinumab 75 or 150 mg SC had significantly higher Assessment in Ankylosing Spondylitis 20 (ASAS20) response rates (59.7% and 60.8%, respectively) versus placebo (28.7%; $p<0.01$) at 16 weeks. When treated with 75 mg SC, 150 mg SC, or placebo, patients who had never received treatment with TNF inhibitors had ASAS20 response rates of 60.0%, 66.3%, and 32.6% and patients whose symptoms did not respond to previous TNF treatment had ASAS20 responses of 58.8%, 45.5%, and 18.2%, respectively ($p<0.01$ versus placebo). At week 16, 66.9% of patients in 75 mg SC group and 69.6% in the 150 mg SC group experienced an adverse event, versus 55.7% given placebo; serious adverse event rates were 1.6%, 2.4%, and 4.1%, respectively.[5] In November 2015, top-line long-term safety and efficacy data were released from this trial that suggest the treatment benefit continued through 104 weeks in patients with AS.[6]

In the phase III MEASURE 2 trial, patients (n=219) with active AS who were intolerant to or did not respond to NSAIDs, DMARDs, or TNF inhibitors were given secukinumab administered as one SC loading dose of 75 or 150 mg once weekly for 4 weeks, followed by 1 SC injection every 4 weeks. Patients given secukinumab 150 mg had significantly higher ASAS20 response rates than patients given placebo (61.1% vs. 27.0%; $p<0.01$) at week 16. Higher ASAS20 rates were reported for secukinumab 150 mg versus placebo in patients who had never received TNFs or patients who did not respond to previous TNF therapy (68.9% vs. 31.1% and 48.1% vs. 20.7%, respectively; both $p<0.05$). Improved ASAS40 rates were also reported (44.4% vs. 17.8% and 22.2% vs. 0%, respectively; both $p<0.05$) at 16 weeks. At 16 weeks, patients who received secukinumab 75 mg did not have significant improvements in ASAS20 or Assessment in Ankylosing Spondylitis 40 (ASAS40) responses compared with patients who received placebo. Similar adverse event rates were reported for secukinumab 75 mg (57.5%), 150 mg (62.5%), and placebo (63.5%) groups up to

week 16. Serious adverse events were reported in 5.5% of the secukinumab 75 mg group, 5.6% of the 150 mg group, and 4.1% of the placebo group.[7] Recently, top-line long-term safety and efficacy data were released for this trial that suggest secukinumab's treatment benefit continued through 104 weeks in patients with AS.[8]

Manufacturer and regulatory status: Novartis International AG (Basel, Switzerland) is developing secukinumab for treating active AS in patients who are intolerant to or have had an inadequate response to NSAIDs, DMARDs, or TNF inhibitor therapy.[9] The company submitted global regulatory submissions for an AS indication, as well as a psoriatic arthritis indication, in 2015.[10]

In January 2015, the U.S. Food and Drug Administration (FDA) approved secukinumab for treating adults with moderate-to-severe plaque psoriasis, a skin condition.[11]

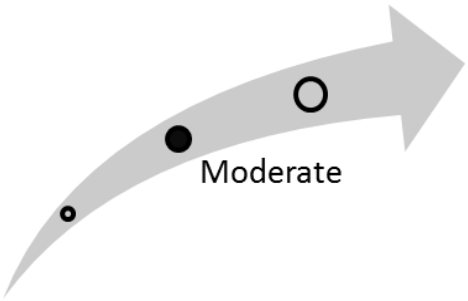
Diffusion and cost: The retail cost of a single carton (1 preloaded pen-injector) of secukinumab 150 mg/mL is reportedly about $3,900, which would be administered once every 4 weeks for treating AS.[12]

Because secukinumab is not yet approved by FDA for treating AS, no coverage, coding, or payment information is available. However, third-party payers would likely consider coverage in appropriate patients. For example, one third-party payer, Aetna, covers the TNF inhibitor adalimumab (Humira®) for treating AS in patients who have an inadequate response to two or more NSAIDs.[13] Payers are likely to cover secukinumab for treating active AS in patients who have had an inadequate response to two or more NSAIDs or patients who have had an inadequate response to TNF inhibitors.

Clinical Pathway at Point of This Intervention

AS treatment focuses on physical therapy and exercise to preserve range of motion and manage pain and stiffness, combined with NSAIDs to reduce inflammation and slow disease progression.[14] Some patients may also be prescribed the immunosuppressive therapies sulfasalazine or methotrexate to suppress long-term inflammation in joints other than the spine. Corticosteroids may be used intermittently to control inflammation. Patients whose symptoms do not respond to conservative therapy or have a higher level of spinal inflammation may be prescribed a TNF inhibitor to decrease inflammation and improve spinal mobility.[14] Secukinumab could be used in place of a TNF inhibitor or in patients whose condition does not respond to therapy with a TNF inhibitor.

Figure 1. Overall high-impact potential: secukinumab (Cosentyx) for treatment of ankylosing spondylitis



Experts commenting on this intervention stated that a significant unmet need exists for patients with AS whose disease does not respond to existing therapies. However, the experts thought that long-term efficacy data are needed to determine secukinumab's true treatment value. Of note, long-term safety and efficacy data were released after we solicited expert comments on this intervention;

these data are not considered in the comments below and may improve experts' opinions on secukinumab's potential impact in patients with AS. The experts also called for randomized controlled trials to compare secukinumab and existing therapies, such as TNF inhibitors. They thought high treatment costs would limit patient access to secukinumab if third-party payers do not cover the drug or if it is covered as a step therapy. Based on this input, as well as the recent data on which we did not receive expert comments, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[15-20] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for patients with treatment-refractory AS, stated the experts. Basing their opinions on available data, the experts generally thought that secukinumab could address this unmet need. However, some were concerned about the reported adverse events.[15,18] Some experts also wanted to see more clinical studies that directly compare secukinumab to other agents, such as TNF inhibitors, as well as long-term functional outcomes.[15,17,18]

Acceptance and adoption: Clinicians are likely to accept secukinumab as a new treatment option for AS, the experts opined. Patients with refractory AS are also likely to accept a new treatment option; one research expert noted that patients may even accept long-term adverse events to avoid AS disease progression.[17]

Health care delivery infrastructure and patient management: As a self-injectable medication, secukinumab is not expected to cause a significant shift in health care delivery infrastructure or patient management. The experts commented that the estimated costs for the drug were substantial; however, better AS management could reduce the need for clinician visits and physical therapy. Reduced hospitalizations, surgical procedures, rehabilitation, and reduced use of orthotics could also offset the cost of secukinumab treatment.[19]

Health disparities: Experts offered mixed comments on the impact of secukinumab on health disparities. Secukinumab could be more expensive than existing options, which may render the drug inaccessible to some patients with AS, some experts thought. Additionally, an expert with a research perspective and another with a health systems perspective noted that the initial use of secukinumab as an IV infusion would require regular clinical visits, which could limit some patients' access to care.[16,17] However, some experts thought that third-party payers would cover the drug, which would not affect health disparities unless patients have high copayments or inadequate insurance coverage.[18,19]

Gout Intervention

Lesinurad for Treatment of Hyperuricemia and Allopurinol-Refractory Gout

Unmet need: Hyperuricemia is thought to be the most important risk factor for developing gout.[21] About 47% of patients with gout do not achieve target goals for serum uric acid (sUA) levels (<6 mg/dL) with the standard of care, the xanthine oxidase inhibitors allopurinol and febuxostat. About 90% of patients with gout are said to have insufficient excretion of uric acid, which could be due to genetic defects in renal transporters of uric acid.[22] About 70% of uric acid excretion occurs in the kidney.[21] Human urate transporter 1 (URAT1) is an organic anion transporter involved in controlling the reabsorption of uric acid from the proximal renal tubules. Only about 30% of patients achieve overall gout control, suggesting an unmet need exists for additional options for gout control.[23]

Intervention: Lesinurad is a selective inhibitor of URAT1 intended to promote urinary excretion of uric acid, leading to improvements in hyperuricemia.[24] Because lesinurad purportedly improves sUA excretion, it is thought to complement use of xanthine oxidase inhibitors, which decrease uric acid production.[22] In phase III trials, lesinurad was administered orally in doses of 200 or 400 mg, once daily in combination with allopurinol or febuxostat,[25,26] or 400 mg, once daily, as monotherapy in patients with an intolerance or contraindication to xanthine oxidase inhibitors.[27]

Clinical trials: Four phase III trials have been completed that evaluated lesinurad in combination with the xanthine oxidase inhibitors allopurinol or febuxostat or as monotherapy in patients unable to tolerate xanthine oxidase inhibitors.

In two replicate phase III trials, CLEAR 1 (n=603) and CLEAR 2 (n=610), patients received lesinurad 200 or 400 mg or placebo daily in combination with allopurinol. Patients had sUA levels of 6.5 mg/dL or higher at screening, were on stable allopurinol doses (≥300 mg or ≥200 mg in patients with moderate renal impairment), and had a history of at least 2 gout flares in the prior 12 months. In the CLEAR 1 trial, patients were given lesinurad 200 or 400 mg, and 54% and 59%, respectively, achieved the sUA target of less than 6.0 mg/dL by month 6, compared with 28% of patients treated with allopurinol and placebo ($p<0.0001$).[25] In the CLEAR 2 trial, patients were also treated with lesinurad 200 or 400 mg, and 55% and 67%, respectively, achieved the sUA target by month 6, compared with 23% of patients treated with allopurinol and placebo ($p<0.0001$).[25] Combination therapy in both trials did not significantly reduce the reported number of gout flares or number of patients with complete tophus resolution.[28] The most common adverse events reported in the two studies were back pain, nasopharyngitis, and upper respiratory tract infection.[26]

In the phase III, randomized, double-blind CRYSTAL trial (n=324), patients with gout, sUA levels of 6.0 mg/dL or more, and at least 1 measurable tophus received lesinurad 200 or 400 mg in combination with oral febuxostat (80 mg) or febuxostat with placebo. Reported data showed that more patients treated with lesinurad and febuxostat achieved the target sUA-level goal of less than 5.0 mg/dL at month 6 than did patients treated with febuxostat alone ($p<0.0001$). Patients treated with lesinurad 200 mg and febuxostat did not achieve a statistically significant improvement at month 6 ($p=0.13$).[26] The most common adverse events reported in this trial were arthralgia, nasopharyngitis, and upper respiratory tract infection.[26]

In the phase III, randomized, double-blind LIGHT trial (n=214), patients with gout, sUA levels of 6.5 mg/dL or higher, and an intolerance or contraindication to a xanthine oxidase inhibitor were given lesinurad 400 mg or placebo, once daily. Data from the manufacturer showed a significantly higher proportion of patients receiving lesinurad achieved the sUA-level goal of less than 6.0 mg/dL at 6 months than did patients given placebo.[27] Use of lesinurad alone resulted in more patients experiencing elevated serum creatinine levels and renal adverse events, including serious events,

than patients given placebo. Other adverse events commonly reported in the lesinurad monotherapy group included constipation, diarrhea, and nausea.[27] Some preliminary evidence suggests lesinurad could increase the risk of renal complications.[29]

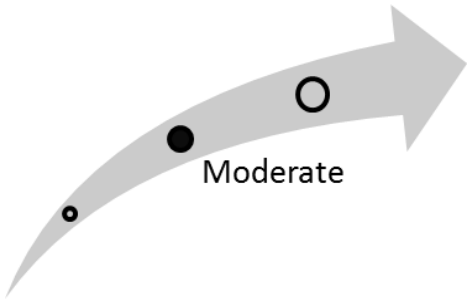
Manufacturer and regulatory status: Ardea Biosciences, a subsidiary of AstraZeneca (London, UK), makes lesinurad. The company has filed regulatory submissions for lesinurad 200 mg as a once-daily, chronic, combination therapy with xanthine oxidase inhibitors for treating gout-related hyperuricemia; it does not intend to pursue approval of lesinurad as a monotherapy. In October 2015, the FDA Arthritis Advisory Committee recommended approval of lesinurad for treating gout-related hyperuricemia; a decision date is set for December 29, 2015.[30]

Diffusion and cost: Our searches found no information about the expected cost of lesinurad, if it is approved. However, according to one financial analyst, annual sales of lesinurad could reach $582 million in the year 2020.[28] About 10% of patients with chronic gout could be prescribed lesinurad, according to an April 2012 survey of U.S. rheumatologists conducted by health care consultant Decision Resources Group.[31] If approved, lesinurad would probably be covered by third-party payers similarly to other uric acid–lowering drugs for treating or preventing gout, although if the drug is more costly than alternatives, prior authorization and a tiered approach could be used.

Clinical Pathway at Point of This Intervention

Patients with gout are treated with a goal of ending the pain of acute flares, preventing future attacks, and preventing formation of tophi and kidney stones. Therapy for acute flares consists of NSAIDs, corticosteroids, and colchicine. Diet and lifestyle modifications (e.g., reducing alcohol and dietary purine intake as well as weight loss) may help prevent future attacks. Preventive therapy with the xanthine oxidase inhibitors allopurinol or febuxostat to lower blood sUA levels is also used in patients with recurrent acute flares or chronic gout.[32,33] Corticosteroids may also be prescribed, as well as drugs that increase uric acid excretion (e.g., colchicine, pegloticase, probenecid). Lesinurad could be used in combination with xanthine oxidase inhibitors for patients in whom sUA levels are inadequately reduced despite therapy.[25-27]

Figure 2. Overall high-impact potential: lesinurad for treatment of hyperuricemia and allopurinol-refractory gout



Experts commenting on this intervention stated that a significant unmet need exists for new treatment options to help patients with gout improve their sUA levels, even though several treatment options are available to address acute flares and manage chronic gout. Lesinurad, which increases uric acid excretion, showed promise in reducing sUA levels when used in combination with xanthine oxidase inhibitors. The experts noted that lesinurad uptake could be limited by concern about adverse events, such as kidney complications, which ongoing clinical trials are intended to provide additional data on. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health administration backgrounds, offered perspectives on this intervention.[34-40] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A moderate unmet need exists for treatments to enable patients with gout to reach sUA level goals, stated the experts. One clinician noted that only one therapy (probenecid) is available that could potentially address the significant problem of uric acid underexcretion, but no evidence-based data exist to support its use.[40] Based on the available data, experts generally thought that lesinurad could address the unmet need by significantly lowering sUA levels when used in combination with febuxostat or allopurinol. However, another expert with a clinical background stated that more data are needed to determine whether increasing uric acid excretion through use of lesinurad would lead to a reduction in morbidity or mortality in patients with gout.[37]

Acceptance and adoption: Most experts thought that clinicians are likely to accept lesinurad as a new option to help patients with gout lower their sUA levels; patients would likely accept lesinurad as a new, once-daily oral treatment option if the drug is effective and its cost is similar to other agents. However, a clinical expert noted that patient and clinician adoption of lesinurad may depend on the drug's long-term safety, which has yet to be determined.[37]

Health care delivery infrastructure and patient management: As an oral medication, lesinurad is not expected to cause a significant shift in health care delivery infrastructure or patient management. However, better gout management could reduce hospitalizations and renal or cardiovascular complications from acute gout flares, reducing demands on the system. Reducing hospitalizations associated with flares could also provide cost offsets from treatment with lesinurad.[38,40] Two research experts noted concerns over renal adverse events, which could require additional monitoring while patients are taking lesinurad.[35,38]

Health disparities: Experts offered mixed comments on the effect of lesinurad on health disparities. Some experts thought that as a new drug, lesinurad would be more expensive than existing options. Patients who have trouble affording existing gout treatments could have trouble paying for lesinurad; payers may not cover a newer, more expensive drug, adding to disparities.[36,37,39] However, two experts stated that because a higher incidence of gout is observed in black males, lesinurad could reduce health disparities in this patient population if it provides a more effective treatment option.[34,39]

Psoriatic Arthritis Intervention

Secukinumab (Cosentyx) for Treatment of Psoriatic Arthritis

Unmet need: In a subset of patients with psoriatic arthritis (PsA), the disease can progress to severe and painful symptoms that, without effective treatment, can lead to deformity and disability of the hands and fingers. Some patients' symptoms do not respond adequately to NSAIDs, conventional DMARDs, or biologic DMARDs such as TNF inhibitors; thus, additional treatment options are needed to manage PsA in these patients. In a small proportion of patients, severe disease develops in their hands, feet, and spine, which can lead to deformities and disability.

Intervention: Secukinumab (Cosentyx) is a fully human monoclonal antibody antagonist for interleukin-17 (IL-17A). IL-17 is a cytokine purportedly involved in developing delayed-type hypersensitivity reactions. These effects are thought by investigators to be mediated by increased chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By instead blocking the effects of IL-17–localized autoimmune reactions, PsA pathogenesis could be limited while minimizing the systemic immunosuppression associated with TNF blockers, a class of biologic agents that are part of the standard of care for PsA.[41] In phase III clinical trials, secukinumab was administered by SC injection 75, 150, or 300 mg, once every 4 weeks,[42] or as 3 loading doses by IV infusion 10 mg/kg, at baseline, 2 weeks, and 4 weeks, followed by one SC injection of 75 mg or 150 mg, every 4 weeks.[43]

Clinical trials: Data are available for a completed phase III trial (FUTURE 1) and an ongoing phase III clinical trial (FUTURE 2) evaluating secukinumab in patients who have PsA.

In the FUTURE 1 trial, patients (n=606) with active, moderate-to-severe PsA, including those who were intolerant to or did not respond to TNF inhibitors, were given secukinumab as an IV infusion 10 mg/kg, in three loading doses, at baseline, 2 weeks, and 4 weeks, followed by one SC injection (75 or 150 mg) every 4 weeks. Patients receiving secukinumab 75 mg and 150 mg SC had significantly higher American College of Rheumatology criteria for 20% improvement (ACR20) response rates (50.5% and 50.0%, respectively) versus placebo (17.3%; $p<0.0001$) at 24 weeks. Using an observed analysis, patients treated with secukinumab 75 mg had ACR 20/50/70 responses of 66.9%, 38.4% and 25.6%, respectively; and patients treated with secukinumab 150 mg SC has response rates of 69.5%, 50.0% and 28.2%, respectively, at 52 weeks. Secukinumab demonstrated superiority to placebo in the ACR20/50/70 measure in patients naïve to TNF inhibitors or patients whose symptoms did not respond to previous TNF inhibitor therapy at week 24. The effect was maintained through week 52. Adverse events/nonfatal serious adverse events rates were 78.1%/8.6% and 82.4%/12.9% in patients who received secukinumab 75 mg or 150 mg, respectively, at any point in the study.[43] Recently, top-line long-term safety and efficacy data were released for this trial that suggest secukinumab's treatment benefit continued through 104 weeks in patients with PsA.[44]

In the FUTURE 2 trial, patients (n=397) with active PsA, including those who were intolerant to or did not respond to TNF inhibitors, were given secukinumab as one SC loading dose of 75, 150, or 300 mg at baseline, then once weekly for 4 weeks, followed by one SC injection every 4 weeks. Patients receiving secukinumab 75, 150, or 300 mg SC had significantly higher ACR20 response rates (29.3%, 51.0%, and 54.0%, respectively) than did patients treated with placebo (15.3%; $p<0.05$ for 75 mg; $p<0.0001$ for 150 and 300 mg) at 24 weeks. Efficacy was observed with secukinumab 150 mg and 300 mg irrespective of prior TNF inhibitor treatment. Patients treated with secukinumab or placebo reported similar rates of overall adverse events: 53.8% of patients in the pooled secukinumab group and 58.2% of patients in the placebo group reported an adverse event. Serious adverse events were reported in 3.3% and 2.0% of patients, respectively, up to week 16.[42] Recently, top-line long-term safety and efficacy data were released for this trial that suggest secukinumab's treatment benefit continued through 52 weeks in patients with PsA.[45]

Manufacturer and regulatory status: Novartis International AG (Basel, Switzerland) is developing secukinumab for treating patients with active PsA who are intolerant to or have had an inadequate response to NSAIDs, DMARDs, or TNF inhibitor therapy.[9] In September 2015, the company announced that it had filed global regulatory submissions for a PsA indication as well as an ankylosing spondylitis (AS) indication.[10]

In January 2015, FDA approved secukinumab for treating adults who have moderate-to-severe plaque psoriasis, the skin condition.[11]

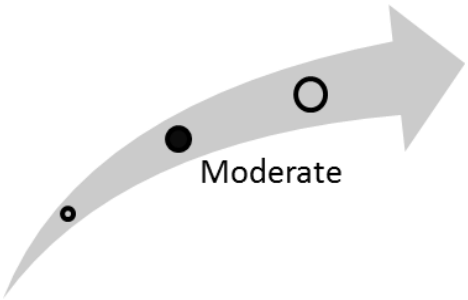
Diffusion and cost: The retail cost of a single carton (1 preloaded pen-injector) of secukinumab 150 mg/mL is reportedly about $3,900, which could be administered once every 4 weeks for treating PsA.[12]

Because secukinumab is not yet approved for treating PsA, no coverage, coding, or payment information is available for this indication; however, the drug would likely be available for coverage once approved. Private third-party payers would likely consider coverage in appropriate patients. For example, one third-party payer, Aetna, covers TNF inhibitors apremilast (Otezla®) and ustekinumab (Stelara®) for treating patients with active nonaxial PsA who have had an inadequate response to methotrexate, or if methotrexate is contraindicated or not tolerated, or who have had an inadequate response to another nonbiologic DMARD. Aetna also considers these treatments medically necessary for patients with active axial PsA whose symptoms have not responded adequately to two or more NSAIDs. However, it considers the use of two or more biologic therapies in combination for treating PsA to be investigational and so does not cover that indication. Additionally, the payer covers secukinumab for adults with moderate-to-severe chronic plaque psoriasis who meet specified treatment criteria.[46]

Clinical Pathway at Point of This Intervention

No cure is available for PsA; treatment focuses on controlling symptoms. Treatment typically consists of NSAIDs, conventional DMARDs, and biologic DMARDs such as TNF inhibitors.[47] Up to 45% of patients with PsA do not respond to their current treatments.[48] Secukinumab could be used in place of a TNF inhibitor or in patients whose condition does not respond to TNF-inhibitor therapy.

Figure 3. Overall high-impact potential: secukinumab (Cosentyx) for treatment of psoriatic arthritis



Overall, experts commenting on secukinumab stated that the drug could potentially fill an unmet need for patients with PsA whose condition does not respond to available therapies. However, the experts wanted to see longer-term efficacy data, as well as direct comparisons to existing therapies such as TNF inhibitors. Of note, long-term safety and efficacy data were released after we solicited expert comments on this intervention; these data are not considered in the comments below and may improve experts' opinions on secukinumab's potential impact in patients with PsA because the data are longer term. The drug's high cost could limit patient access if third-party payers do not cover

the majority of treatment costs. However, these costs may be offset by decreased use of other health care resources. Based on this input, as well as the recent data on which we did not receive expert comments, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[49-54] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for patients with PsA whose disease is refractory to existing therapies, stated the experts. Based on available data, experts generally thought that secukinumab could address this unmet need. However, some experts wanted to see more clinical data that directly compare secukinumab to competing TNF inhibitors.[50-52]

Acceptance and adoption: Clinicians are likely to accept secukinumab as a new option to help patients with PsA manage their disease, the experts opined. The experts thought that patients with PsA would accept this option, especially those whose disease has not responded to other therapies.[51,53] Patients are also likely to accept secukinumab because of the simple self-administration of the drug.[50,52]

Health care delivery infrastructure and patient management: As a self-injected medication, secukinumab is not expected to significantly shift health care delivery or change infrastructure or patient management. The experts commented that the estimated costs were substantial, especially if secukinumab is effective in patients who do not respond to other treatments because it would add to total costs. However, one clinician noted that better PsA management could reduce the need for clinician visits, other prescriptions, inpatient stays in rehabilitation facilities, and use of orthotic devices, offsetting the direct cost of secukinumab.[52]

Health disparities: Experts offered mixed comments on the impact of secukinumab on health disparities. One clinical expert noted that he had been analyzing Medicare data on patients with psoriasis and indicated that the data suggest that African Americans with PsA may be less likely to use a biologic drug than Caucasians; however, no reason was provided for this observation.[49] Otherwise, experts thought that treatment with secukinumab would not exacerbate health disparities unless patients have high out-of-pocket costs and/or inadequate insurance coverage.[52,53]

Rheumatoid Arthritis Intervention

Baricitinib for Treatment of Rheumatoid Arthritis

Unmet need: A cure for rheumatoid arthritis (RA) does not exist; available treatments are used for managing symptoms. Some patients with RA do not adequately respond to NSAIDs, conventional DMARDs such as methotrexate, or biologic DMARDs such as TNF inhibitors; thus, additional treatment options are needed to manage RA symptoms in these patients.

Intervention: Baricitinib is a Janus kinase (JAK) inhibitor that inhibits JAK1 and JAK2, two of the four members of the JAK family. Inhibiting these kinases blocks the downstream effects of multiple pro-inflammatory cytokines implicated in RA pathogenesis, including granulocyte-macrophage colony stimulating factor, interleukin (IL)-6, IL-12, IL-15, IL-23, and interferon gamma.[55] In preclinical arthritis models, baricitinib purportedly had significant anti-inflammatory effects as well as preserving bone and cartilage without humoral immunity suppression or other adverse hematological effects.[56] Another JAK inhibitor, tofacitinib (Xeljanz®), which inhibits JAK1, JAK2, and JAK3, is available for treating RA, but may cause serious adverse events (e.g., cancer and opportunistic infections).[55] In initial phase III clinical trials, baricitinib 2 or 4 mg was administered orally, once daily, for 24 weeks;[57,58] subsequent trials evaluated baricitinib 4 mg once daily for 52 weeks.[59-62]

Clinical trials: Data are available for four completed phase III trials (RA-BEACON, RA-BUILD, RA-BEAM, and RA-BEGIN) evaluating baricitinib in patients who have RA.

In the phase III RA-BEACON trial, patients (n=527) with moderate-to-severe RA who did not respond to treatment with at least 1 TNF inhibitor and at least 1 conventional DMARD were given baricitinib 2 or 4 mg, orally, for 24 weeks. After 12 weeks of treatment, patients receiving baricitinib 4 mg had significantly higher ACR20 response rates (55%) than patients receiving placebo (27%; $p<0.001$); data for the 2 mg dose were not reported. Treatment benefit continued through 24 weeks for baricitinib 4 mg. Rates of treatment-emergent adverse events were 71%, 77%, and 64% for baricitinib 2 mg, baricitinib 4 mg, and placebo, respectively; serious adverse event rates were 4%, 10%, and 7%, respectively. No opportunistic infections or cases of tuberculosis (TB) occurred. Two nonmelanoma skin cancers (NMSC) and 2 major adverse cardiovascular events, including 1 death (stroke), were seen with baricitinib 4 mg.[63]

In the RA-BUILD trial, patients (n=684) with moderate-to-severe RA who were intolerant to or did not respond to at least 1 conventional DMARD were given baricitinib 2 or 4 mg, orally, for 24 weeks. After 12 weeks of treatment, patients receiving baricitinib 4 mg had significantly higher ACR20 response rates (62%) than patients receiving placebo (40%; $p<0.001$); ACR20 data for the 2 mg dose were not reported. Treatment benefit continued through 24 weeks for baricitinib 4 mg. Rates of serious adverse events were 3%, 5%, and 5%, for baricitinib 2 or 4 mg or placebo, respectively; treatment-emergent adverse event rates were not reported. No opportunistic infections occurred; one case of TB and one case of NMSC occurred in the baricitinib 4 mg group.[64]

The RA-BEAM trial compared baricitinib's safety and efficacy to that of its potential competitor adalimumab, a TNF inhibitor. Patients (n=1,305) with moderate-to-severe RA who did not respond to methotrexate treatment were given 1 of the following 3 treatment regimens: baricitinib 4 mg, orally, for 52 weeks; adalimumab 40 mg, SC, for 50 weeks; or placebo. After 12 weeks of treatment, patients receiving baricitinib had significantly higher ACR20 response rates (70%) than patients receiving placebo (40%; $p<0.001$) or adalimumab (61%; $p<0.05$). Treatment benefit continued through 24 weeks for baricitinib 4 mg. Rates of treatment-emergent adverse events after 12 weeks were 53%, 51%, and 47% for baricitinib, adalimumab, and placebo, respectively; serious adverse event rates after 12 weeks were 2.3%, 1.2%, and 2.7%, respectively. One case of TB occurred in the adalimumab group.[65]

In the RA-BEGIN trial comparing baricitinib's safety and efficacy to methotrexate, patients (n=1,305) with early active RA who had limited or no treatment experience with methotrexate were given 1 of the following 3 regimens: baricitinib 4 mg, orally, once daily for 52 weeks; methotrexate 10–20 mg, orally, once weekly for 52 weeks; or baricitinib 4 mg, orally, once daily plus methotrexate 10–20 mg, orally, once weekly for 52 weeks. After 24 weeks, patients receiving baricitinib monotherapy or baricitinib/ methotrexate combination therapy had significantly higher ACR20 response rates (77% and 78%, respectively) than patients receiving methotrexate monotherapy (62%; $p<0.01$ for both groups). Rates of treatment-emergent adverse events after 24 weeks were 65%, 64%, and 67% for methotrexate, baricitinib, and baricitinib/methotrexate, respectively; serious adverse event rates after 24 weeks were 3.8%, 3.1%, and 3.7%, respectively. Two cases of malignancy occurred in the baricitinib/methotrexate group.[66]

Manufacturer and regulatory status: Eli Lilly and Co. (Indianapolis, IN), in a global license and collaboration agreement with Incyte Corp. (Wilmington, DE), is developing baricitinib for treating patients with RA who are either naïve to existing treatments for RA, or who have had an inadequate response to one or more of these treatments.[67]

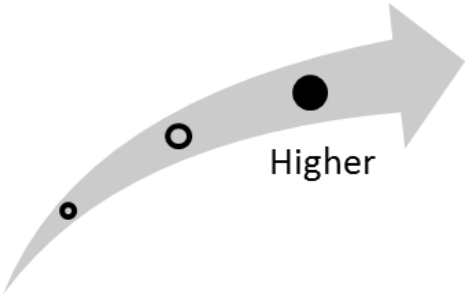
Diffusion and cost: Our searches found no information regarding baricitinib's cost. Tofacitinib, an oral JAK inhibitor approved for treating RA, can be used as a benchmark; tofacitinib reportedly costs about $2,900 per month.[68] If approved, baricitinib could be priced similarly to tofacitinib.

Because baricitinib is not approved for treating RA, no coverage, coding, or payment information is available. Private third-party payers would likely consider coverage in patients who did not respond to existing therapies for RA.

Clinical Pathway at Point of This Intervention

No cure is available for RA; treatment focuses on controlling symptoms using NSAIDs, conventional DMARDs, and biologic DMARDs such as TNF inhibitors.[69,70] Additionally, tofacitinib is available for treating RA, but patients treated with this JAK inhibitor may develop opportunistic infections, TB, or cancer.[55] Collectively, these treatments are not always effective in patients with RA. Baricitinib could potentially be used instead of tofacitinib or a TNF inhibitor in patients who are naïve to treatment with biologic DMARDs, and may also be used in patients whose symptoms have not improved after being treated with one or more existing therapies.

Figure 4. Overall high-impact potential: baricitinib for treatment of rheumatoid arthritis



Overall, experts commenting on baricitinib stated that the drug could potentially fill an unmet need for patients with RA who have had an inadequate response to available therapies. Of note, experts did not comment on data from the RA-BEAM and RA-BEGIN trials that compared baricitinib to the DMARDs methotrexate and adalimumab, because these data were not available at the time comments were solicited. However, most experts thought that such data would positively affect the potential of baricitinib, should the drug demonstrate increased efficacy compared to its

potential competitors. The experts also thought that long-term safety and efficacy data for baricitinib are needed. The drug's high cost could limit patient and clinician adoption if third-party payers do not cover the majority of treatment costs. However, these costs may be offset by decreased use of other health care resources. Based on this input, as well as the additional data showing baricitinib's improved efficacy in treating RA versus comparators (on which we have not yet received comments), our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[71-76] We have organized the following discussion according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for patients with RA whose disease is refractory to existing therapies, stated the experts. Based on the available data, experts generally thought that baricitinib could address this unmet need.

Acceptance and adoption: Clinicians are likely to accept baricitinib as a new option to help patients with RA manage their disease, the experts opined. Generally, the experts thought that patients would also accept baricitinib, especially those whose disease has not responded to other therapies. One clinician noted that patients receiving tofacitinib may be prescribed baricitinib instead, due to data suggesting that baricitinib has an improved safety profile versus tofacitinib. However, the same expert noted that if third-party payers limit coverage of baricitinib or place the drug in a more expensive tier than existing treatments, these practices could limit patient and clinician adoption.[75]

Health care delivery infrastructure and patient management: As an oral medication, baricitinib is not expected to significantly shift health care delivery or change infrastructure or patient management. The experts commented that the estimated costs were substantial, especially if baricitinib is prescribed after patients do not respond to existing first- and second-line treatments, adding to total costs. However, one research expert noted that baricitinib potentially could delay disease progression, and therefore prevent or delay assisted living needs associated with severe RA.[72]

Health disparities: Experts offered mixed comments on the impact of baricitinib on health disparities. Some experts thought that baricitinib would not affect health disparities if the drug were to be priced similarly to and used in place of available treatments,[71,73,75] but several others noted that baricitinib could exacerbate health disparities if patients have high out-of-pocket costs and/or inadequate insurance coverage.[72,73,76]

References

1. Brent LH. Ankylosing spondylitis and undifferentiated spondyloarthropathy. In: Medscape [internet]. New York (NY): WebMD LLC; 2014 Nov 05 [accessed 2015 Jan 13]. [11 p]. Available: http://emedicine.medscape.com/article/332945-overview.

2. Novartis AIN457 (secukinumab) meets primary endpoint in two phase III studies in ankylosing spondylitis, a debilitating joint condition of the spine. [internet]. Basel (Switzerland): Novartis AG; 2014 Oct 23 [accessed 2015 Jan 07]. [4 p]. Available: http://www.novartis.com/newsroom/media-releases/en/2014/1864939.shtml.

3. Novartis Pharmaceuticals. 16 week efficacy and 2 year long term safety and efficacy of secukinumab in patients with active ankylosing spondylitis (MEASURE 1). In: ClinicalTrials.gov [database online]. Bethesda (MD): U.S. National Library of Medicine (NLM); 2000- [accessed 2015 Feb 24]. [4 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01358175 NLM Identifier: NCT01358175.

4. Novartis Pharmaceuticals. 16 week efficacy and 5 year long term efficacy, safety and tolerability of secukinumab in patients with active ankylosing spondylitis (MEASURE2). In: ClinicalTrials.gov [database online]. Bethesda (MD): U.S. National Library of Medicine (NLM); 2000- [accessed 2015 Feb 24]. [4 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01649375 NLM Identifier: NCT01649375.

5. Baeten DL, Braun J, Baraliakos X, et al. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a 52-week phase 3 randomized placebo-controlled trial with intravenous loading and subcutaneous maintenance dosing. In: American College of Rheumatology (ACR) Annual Meeting; 2014 Nov 14-19; Boston (MA). Also available: http://acrabstracts.org/abstracts/secukinumab-a-monoclonal-antibody-to-interleukin-17a-significantly-improves-signs-and-symptoms-of-active-ankylosing-spondylitis-results-of-a-52-week-phase-3-randomized-placebo-controlled-trial-with/.

6. Baeten D, Braun J, Sieper J, et al. Secukinumab provides sustained improvements in the signs and symptoms of active ankylosing spondylitis: 2-year efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled trial. In: 2015 American College of Rheumetology (ACR) Annual Meeting; 2015 Nov 6-11; San Francisco (CA). Also available: http://acrabstracts.org/abstract/secukinumab-provides-sustained-improvements-in-the-signs-and-symptoms-of-active-ankylosing-spondylitis-2-year-efficacy-and-safety-results-from-a-phase-3-randomized-double-blind-placebo-controlled/.

7. Sieper J, Braun J, Baraliakos X, et al. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a phase 3, randomized, placebo-controlled trial with subcutaneous loading and maintenance dosing. In: American College of Rheumatology (ACR) Annual Meeting; 2014 Nov 14-19; Boston (MA). Also available: http://acrabstracts.org/abstracts/secukinumab-a-monoclonal-antibody-to-interleukin-17a-significantly-improves-signs-and-symptoms-of-active-ankylosing-spondylitis-results-of-a-phase-3-randomized-placebo-controlled-trial-with-subcu/.

8. Braun J, Deodhar AA, Sieper J, et al. In: 2015 American College of Rheumetology (ACR) Annual Meeting; 2015 Nov 6-11; San Francisco (CA). Also available: http://acrabstracts.org/abstract/secukinumab-significantly-improves-signs-and-symptoms-of-active-ankylosing-spondylitis-52-week-results-from-a-randomized-double-blind-placebo-controlled-phase-3-trial-with-subcutaneous-loading-and/.

9. Novartis presents ground-breaking phase III results showing AIN457 (secukinumab) significant efficacy in ankylosing spondylitis patients. [internet]. Basel (Switzerland): Novartis AG; 2014 Nov 15 [accessed 2015 Feb 24]. [4 p]. Available: http://www.novartis.com/newsroom/media-releases/en/2014/1871694.shtml.

10. Novartis announces NEJM publication of secukinumab Phase III data confirming significant efficacy in patients with psoriatic arthritis. [internet]. Basel (Switzerland): Novartis; 2015 Sep 30 [accessed 2015 Nov 20]. [3 p]. Available: http://multimediacapsule.thomsonone.com/novartis/novartis-announces-nejm-publication-of-secukinumab-phase-iii-data-in-psa.

11. Novartis announces FDA approval for first IL-17A antagonist Cosentyx (secukinumab) for moderate-to-severe plaque psoriasis patients. [internet]. Basel (Switzerland): Novartis AG; 2015 Jan 21 [accessed 2015 May 20]. [4 p]. Available: https://www.novartis.com/news/media-releases/novartis-announces-fda-approval-first-il-17a-antagonist-cosentyxtm-secukinumab.

12. Cosentyx pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Nov 19]. [10 p]. Available: http://www.goodrx.com/cosentyx.

13. Aetna, Inc. Clinical policy bulletin: adalimumab (Humira). Policy number: 0655. [internet]. Hartford (CT): Aetna, Inc.; 2014 Dec 22 [accessed 2015 Feb 24]. [21 p]. Available: http://www.aetna.com/cpb/medical/data/600_699/0655.html.

14. Sheil WC Jr. What are ankylosing spondylitis treatment options? [internet]. New York (NY): MedicineNet, Inc.; 2014 Jun 20 [accessed 2015 Feb 24]. [6 p]. Available: http://www.medicinenet.com/ankylosing_spondylitis/page5.htm.

15. Expert Commenter 1015. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1665 - Secukinumab for treatment of ankylosing spondylitis. 2015 Mar 25 [review date].

16. Expert Commenter 403. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1665 - Secukinumab for treatment of ankylosing spondylitis. 2015 Mar 30 [review date].

17. Expert Commenter 427. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1665 - Secukinumab for treatment of ankylosing spondylitis. 2015 Mar 31 [review date].

18. Expert Commenter 1224. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS1665 - Secukinumab for treatment of ankylosing spondylitis. 2015 Apr 24 [review date].

19. Expert Commenter 982. (External, Clinical). Horizon Scanning Structured Comment Form. HS1665 - Secukinumab for treatment of ankylosing spondylitis. 2015 Apr 22 [review date].

20. Expert Commenter 1026. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1665 - Secukinumab for treatment of ankylosing spondylitis. 2015 May 18 [review date].

21. Roddy E, Doherty M. Epidemiology of gout. Arthritis Res Ther. 2010;12(6):223. Also available: http://dx.doi.org/10.1186/ar3199. PMID: 21205285.

22. Ardea Biosciences announces positive top-line results from phase 2b combination study of RDEA594 in allopurinol-refractory gout patients. [internet]. San Diego (CA): Ardea Biosciences, Inc.; 2011 Jan 06 [accessed 2011 Feb 23]. [3 p]. Available: http://investorcenter.ardeabio.com/phoenix.zhtml?c=122089&p=irol-newsArticle&ID=1513841&highlight=.

23. Morlock R, Kern DM, Tunceli O, et al. Rate of serum uric acid (SUA) assessment in gout patients treated with urate-lowering therapy: treating to target?. [internet]. London (UK): AstraZeneca; 2014 Nov 16 [accessed 2014 Dec 08]. [2 p]. Available: http://www.astrazeneca.com.

24. AstraZeneca to acquire Ardea Biosciences for $1 billion (net of existing cash) including lead product lesinurad in Phase III development for gout. [internet]. London (UK): AstraZeneca; 2012 Apr 23 [accessed 2014 Mar 03]. [3 p]. Available: http://www.astrazeneca.com/Media/Press-releases/Article/20120423--astrazeneca-to-acquire-ardea-biosciences.

25. Saag KG, Adler S, Bhakta N, et al. Lesinurad, a novel selective uric acid reabsorption inhibitor, in two phase III clinical trials: combination study of lesinurad in allopurinol standard of care inadequate responders (CLEAR 1 and 2). [internet]. London (UK): AstraZeneca; 2014 Nov 16 [accessed 2014 Dec 08]. [2 p]. Available: http://www.astrazeneca.com.

26. AstraZeneca announces topline results from the Phase III programme of lesinurad in combination with xanthine oxidase inhibitors in gout patients. [internet]. London (CA): AstraZeneca; 2014 Aug 13 [accessed 2014 Aug 13]. [3 p]. Available: http://www.astrazeneca.com/Media/Press-releases/Article/13082014--astrazeneca-announces-topline-results-from-the-phase.

27. AstraZeneca announces top-line results from phase III monotherapy study of lesinurad in gout patients. [internet]. London (UK): AstraZeneca; 2013 Dec 13 [accessed 2014 Mar 03]. [3 p]. Available: http://www.astrazeneca.com/Media/Press-releases/Article/13122013--astrazeneca-announces-topline-results-from-phase-iii.

28. Carroll J. AstraZeneca's PhIII gout data for lesinurad includes a hit, a strikeout and a missing player. [internet]. Washington (DC): FierceMarkets; 2014 Nov 16 [accessed 2014 Dec 08]. [4 p]. Available: http://www.fiercebiotech.com/story/astrazenecas-phiii-gout-data-lesinurad-includes-hit-strikeout-and-missing-p/2014-11-16.

29. Garde D. AstraZeneca may have a gout blockbuster on its hands with lesinurad. [internet]. FierceBiotech; 2014 Feb 14 [accessed 2014 Mar 24]. [4 p]. Available: http://www.fiercebiotech.com/story/astrazeneca-may-have-gout-blockbuster-its-hands-lesinurad/2014-02-14.

30. FDA Advisory Committee recommends the approval of lesinurad for gout patients. [internet]. Wilmington (DE): AstraZeneca; 2015 Oct 23 [accessed 2015 Oct 28]. [2 p]. Available: http://www.astrazeneca-us.com/media/press-releases/Article/20151023--fda-advisory-committee-lesinurad.

31. Surveyed U.S. rheumatologists indicate that they would prescribe Ardea Biosciences' lesinurad to ten percent of their patients with chronic gout. [internet]. Burlington (MA): Decision Resources; 2012 Apr 18 [accessed 2014 Apr 21]. [2 p]. Available: http://decisionresources.com/News-and-Events/Press-Releases/Chronic-Gout-041812.

32. Gout. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2011 Aug 01 [accessed 2014 Apr 21]. [5 p]. Available: http://www.cdc.gov/arthritis/basics/gout.htm.

33. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012 Oct;64(10):1431-46. PMID: 23024028.

34. Expert Commenter 395. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS239 - Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout. 2015 Nov 5 [review date].

35. Expert Commenter 427. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS239 - Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout. 2015 Nov 4 [review date].

36. Expert Commenter 1649. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS239 - Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout. 2015 Nov 3 [review date].

37. Expert Commenter 1706. (External, Clinical). Horizon Scanning Structured Comment Form. HS239 - Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout. 2015 Oct 30 [review date].

38. Expert Commenter 1575. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS239 - Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout. 2015 Nov 6 [review date].

39. Expert Commenter 982. (External, Clinical). Horizon Scanning Structured Comment Form. HS239 - Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout. 2015 Nov 4 [review date].

40. Expert Commenter 1707. (External, Clinical). Horizon Scanning Structured Comment Form. HS239 - Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout. 2015 Nov 20 [review date].

41. Novartis to reveal landmark phase III data for AIN457 (secukinumab) in psoriatic arthritis and ankylosing spondylitis at ACR 2014. [internet]. Basel (Switzerland): Novartis AG; 2014 Nov 10 [accessed 2014 Nov 12]. [4 p]. Available: http://www.novartis.com/newsroom/media-releases/en/2014/1869976.shtml.

42. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17a monoclonal antibody, improves active psoriatic arthritis: 24-week efficacy and safety data from a phase 3 randomized, multicenter, double-blind, placebo-controlled study using subcutaneous dosing. [internet]. Atlanta (GA): American College of Rheumatology; 2014 [accessed 2015 Feb 27]. [4 p]. Available: http://acrabstracts.org/abstracts/secukinumab-a-human-anti-interleukin-17a-monoclonal-antibody-improves-active-psoriatic-arthritis-24-week-efficacy-and-safety-data-from-a-phase-3-randomized-multicenter-double-blind-placebo-contr/.

43. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab, a human anti-interleukin-17a monoclonal antibody, improves active psoriatic arthritis and inhibits radiographic progression: efficacy and safety data from a phase 3 randomized, multicenter, double-blind, placebo-controlled study. [internet]. Atlanta (GA): American College of Rheumatology; 2014 [accessed 2015 Feb 27]. [5 p]. Available: http://acrabstracts.org/abstracts/secukinumab-a-human-anti-interleukin-17a-monoclonal-antibody-improves-active-psoriatic-arthritis-and-inhibits-radiographic-progression-efficacy-and-safety-data-from-a-phase-3-randomize/.

44. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab provides sustained improvements in psoriatic arthritis: 2-year efficacy and safety results from a phase 3 randomized, double-blind, placebo-controlled trial. In: 2015 American College of Rheumetology (ACR) Annual Meeting; 2015 Nov 6-11; San Francisco (CA). Also available: http://acrabstracts.org/abstract/secukinumab-provides-sustained-improvements-in-psoriatic-arthritis-2-year-efficacy-and-safety-results-from-a-phase-3-randomized-double-blind-placebo-controlled-trial/.

45. Kavanaugh A, McInnes IB, Mease PJ, et al. Secukinumab provides sustained improvements in the signs and symptoms of active psoriatic arthritis in anti-TNF-naive patients and those previously exposed to anti-TNF therapy: 52-week results from a randomized, double-blind, placebo-controlled phase 3 trial with subcutaneous dosing. In: 2015 American College of Rheumetology (ACR) Annual Meeting; 2015 Nov 6-11; San Francisco (CA). Also available: http://acrabstracts.org/abstract/secukinumab-provides-sustained-improvements-in-the-signs-and-symptoms-of-active-psoriatic-arthritis-in-anti-tnf-naive-patients-and-those-previously-exposed-to-anti-tnf-therapy-52-week-results-from-a/.

46. Aetna, Inc. Clinical policy bulletin: psoriasis and psoriatic arthritis: biological therapies. Policy number: 0658. [internet]. Hartford (CT): Aetna, Inc.; 2015 Feb 24 [accessed 2015 Feb 27]. [24 p]. Available: http://www.aetna.com/cpb/medical/data/600_699/0658.html.

47. Psoriatic arthritis. In: PubMed Health [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2014 Apr 18 [accessed 2015 Feb 19]. [4 p]. Available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001450/.

48. Armstrong AW, Robertson AD, Wu J, et al. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. JAMA Dermatol. 2013 Oct;149(10):1180-5. Also available: http://dx.doi.org/10.1001/jamadermatol.2013.5264. PMID: 23945732.

49. Expert Commenter 1189. (External, Clinical). Horizon Scanning Structured Comment Form. HS2013 - Secukinumab (Cosentyx) for treatment of psoriatic arthritis. 2015 Apr 30 [review date].

50. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2013 - Secukinumab (Cosentyx) for treatment of psoriatic arthritis. 2015 Apr 14 [review date].

51. Expert Commenter 1242. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2013 - Secukinumab (Cosentyx) for treatment of psoriatic arthritis. 2015 Apr 9 [review date].

52. Expert Commenter 982. (External, Clinical). Horizon Scanning Structured Comment Form. HS2013 - Secukinumab (Cosentyx) for treatment of psoriatic arthritis. 2015 Apr 16 [review date].

53. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2013 - Secukinumab (Cosentyx) for treatment of psoriatic arthritis. 2015 Apr 16 [review date].

54. Expert Commenter 1026. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2013 - Secukinumab (Cosentyx) for treatment of psoriatic arthritis. 2015 May 15 [review date].

55. O'Shea JJ, Kontzias A, Yamaoka K, et al. Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis. 2013 Apr;72:ii111-5. Also available: http://dx.doi.org/10.1136/annrheumdis-2012-202576. PMID: 23532440.

56. Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015 Feb 1;74(2):333-40. Also available: http://dx.doi.org/10.1136/annrheumdis-2014-206478. PMID: 25431052.

57. Eli Lilly and Company. A moderate to severe rheumatoid arthritis study (RA-BEACON). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Nov 20]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01721044 NLM Identifier: NCT01721044.

58. Eli Lilly and Company. A study in moderate to severe rheumatoid arthritis participants (RA-BUILD). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Nov 20]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01721057 NLM Identifier: NCT01721057.

59. Eli Lilly and Company. A study of baricitinib (LY3009104) in participants with rheumatoid arthritis (RA). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Apr 29]. [5 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT02265705 NLM Identifier: NCT02265705.

60. Eli Lilly and Company. An extension study in participants with moderate to severe rheumatoid arthritis (RA-BEYOND). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Apr 29]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01885078 NLM Identifier: NCT01885078.

61. Eli Lilly and Company. A study in participants with moderate to severe rheumatoid arthritis (RA-BEGIN). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Nov 20]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01711359 NLM Identifier: NCT01711359.

62. Eli Lilly and Company. A study in moderate to severe rheumatoid arthritis (RA-BEAM). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Nov 20]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT01710358 NLM Identifier: NCT01710358.

63. Genovese MC, Kremer J, Zamani O, et al. Baricitinib, an oral janus kinase (JAK)1/JAK2 inhibitor, in patients with active rheumatoid arthritis (RA) and an inadequate response to TNF inhibitors: results of the phase 3 RA-beacon study. In: European League Against Rheumatism (EULAR) 2015 Annual Conference; 2015 Jun 10-13; Rome (Italy). Also available: https://b-com.mci-group.com/Abstract/Statistics/AbstractStatisticsViewPage.aspx?AbstractID=246874.

64. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib, an oral janus kinase (JAK)1/JAK2 inhibitor, in patients with active rheumatoid arthritis (RA) and an inadequate response to CDMARD therapy: results of the phase 3 RA-build study. In: European League Against Rheumatism (EULAR) 2015 Annual Conference; 2015 Jun 10-13; Rome (Italy). Also available: https://b-com.mci-group.com/Abstract/Statistics/AbstractStatisticsViewPage.aspx?AbstractID=263899.

65. Taylor PC, Keystone EC, Van der Heije D, et al. Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis (RA) and an inadequate response to background methotrexate therapy: results of a phase 3 study. In: 2015 American College of Rheumetology (ACR) Annual Meeting; 2015 Nov 6-11; San Francisco (CA). Also available: http://acrabstracts.org/abstract/baricitinib-versus-placebo-or-adalimumab-in-patients-with-active-rheumatoid-arthritis-ra-and-an-inadequate-response-to-background-methotrexate-therapy-results-of-a-phase-3-study/.

66. Fleischmann R, Takeuchi T, Schlichting DE, et al. Baricitinib, methotrexate, or baricitinib plus methotrexate in patients with early rheumatoid arthritis who had received limited or no treatment with disease-modifying anti-rheumatic drugs (DMARDs): phase 3 trial results. In: 2015 American College of Rheumetology (ACR) Annual Meeting; 2015 Nov 6-11; San Francisco (CA). Also available: http://acrabstracts.org/abstract/baricitinib-methotrexate-or-baricitinib-plus-methotrexate-in-patients-with-early-rheumatoid-arthritis-who-had-received-limited-or-no-treatment-with-disease-modifying-anti-rheumatic-drugs-dmards-p/.

67. Detailed results demonstrate baricitinib superiority to adalimumab in improving signs and symptoms of rheumatoid arthritis. [internet]. Indianapolis (IN): Eli Lilly and Company; 2015 Nov 8 [accessed 2015 Nov 20]. [3 p]. Available: https://investor.lilly.com/releasedetail.cfm?ReleaseID=941386.

68. Tofacitinib pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Nov 20]. [11 p]. Available: http://www.goodrx.com/tofacitinib?drug-name=tofacitinib.

69. Mayo Clinic staff. Rheumatoid arthritis. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2014 Oct 29 [accessed 2015 Apr 03]. [7 p]. Available: http://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/basics/definition/con-20014868.

70. Centers for Disease Control and Prevention (CDC). Rheumatoid arthritis. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2014 Nov 6 [accessed 2015 Apr 03]. [11 p]. Available: http://www.cdc.gov/arthritis/basics/rheumatoid.htm.

71. Expert Commenter 1573. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1066 - Baricitinib for treatment of rheumatoid arthritis. 2015 Jul 27 [review date].

72. Expert Commenter 1243. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1066 - Baricitinib for treatment of rheumatoid arthritis. 2015 Aug 4 [review date].

73. Expert Commenter 1320. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1066 - Baricitinib for treatment of rheumatoid arthritis. 2015 Jul 27 [review date].

74. Expert Commenter 993. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1066 - Baricitinib for treatment of rheumatoid arthritis. 2015 Jul 30 [review date].

75. Expert Commenter 989. (External, Clinical). Horizon Scanning Structured Comment Form. HS1066 - Baricitinib for treatment of rheumatoid arthritis. 2015 Aug 25 [review date].

76. Expert Commenter 982. (External, Clinical). Horizon Scanning Structured Comment Form. HS1066 - Baricitinib for treatment of rheumatoid arthritis. 2015 Aug 19 [review date].